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•Case report•

# A case of recurrent neuroleptic malignant syndrome

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**Summary:** Neuroleptic malignant syndrome (NMS) is a life-threatening neurologic complication associated with the use of neuroleptic agents and characterized by a distinctive clinical syndrome of fever, rigidity, autonomic nervous system dysfunction and mental status change. This report discusses the clinical presentation, possible etiology, pathogenesis and treatment of one case of recurrent NMS in a middle-aged woman with schizophrenia. NMS occurred after combined treatment with haloperidol and aripiprazole (the first episode) and, four years later, after combined treatment with haloperidol and clozapine (the second episode). This case highlights the need to be particularly cautious in the use of antipsychotic medications in patients with a history of NMS and, whenever possible, to avoid combined treatment with multiple antipsychotic medications in these patients.

## 1. Case history

A 46-year-old female with a four-year history of disorganized speech, lack of impulse control and insomnia was admitted for her first hospitalization in May 2006 at the Sixth People's Hospital of Anqing because her symptoms had exacerbated over the prior two months. After being diagnosed with schizophrenia on admission, she was treated with intramuscular haloperidol 10 mg bid and oral aripiprazole 10 mg bid. After one week of treatment, her temperature rose to 39.8 $^{o}$C and her pulse increased to 110/min. She experienced urinary retention, became disoriented and then lost consciousness. Her muscles became rigid and she showed no spontaneous movement. Blood tests showed a leukocyte level of $14.8\times10^{9}$/L, with a neutrophil percentage of 63.0%. Blood biochemistry found that creatine kinase (CPK) was 1794 u/L, alanine transaminase (ALT) was 139 u/L, and glutamic oxaloacetic transaminase (SGOT) was 128 u/L. The patient was then given a diagnosis of neuroleptic malignant syndrome (NMS). Her antipsychotic medication was stopped immediately and supportive measures were instituted including intravenous fluids and fever reduction therapy. After one week, most of the physical symptoms of NMS abated and her vital signs were stable. The patient was then given clozapine 300 mg/d and sulpiride 400 mg/d. She continued on this medication regime for 2 weeks until discharge from hospital but did not re-experience any of the symptoms of NMS. After discharge, the patient continued to take low doses of clozapine and sulpiride for one year and then gradually converted to monotherapy with clozapine 50 mg/d. Her psychotic symptoms were well controlled and her social function was almost normal.

In April 2012, four years after her first discharge, she was re-admitted with a two-day history of disorganized speech, wandering, aimless behavior, and insomnia. This change apparently had been triggered by an insignificant family problem the day before the symptoms started. On admission, her pulse was regular at 86/min and her respirations were stable. She was uncooperative during the psychiatric interview; she spoke to herself and did not respond to questions appropriately. Her mental status exam showed inappropriate affect, lack of insight and disorganized behavior. She was given the diagnosis of recurrent schizophrenia.

On the first two days of hospitalization she received intramuscular haloperidol 2.5 mg bid; this dosage was increased to 5 mg bid on the 3$^{rd}$ and 4$^{th}$ days of admission, but the haloperidol was then discontinued on the 5$^{th}$ day of admission. Her dose of oral clozapine was maintained at 50 mg/d during the first 4 days of admission and then gradually increased to 200 mg/d by the seventh day of admission. On the 8$^{th}$ day of admission, she developed salivation, sweating, and had a fever of 38.5 $^{o}$C; by the 9$^{th}$ day of admission she had become disoriented and then lapsed into unconsciousness with rigid muscles and no spontaneous movement. Blood tests showed a leukocyte level of $10.5\times10^{9}$/L, with a neutrophil percentage of 78.7%. Blood biochemistry showed that her CPK was 1878 u/L, ALT was 76 u/L, and SGOT was 65 u/L. Her chest X-ray result was normal. The patient was then diagnosed as having recurrent NMS. The clinical management of this episode of NMS was similar to that used in the first episode – antipsychotic medication was stopped and she was given supportive

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and symptomatic treatment – but this time she was also treated with bromocriptine mesylate 10 mg/d. After one week, most of her NMS symptoms resolved and her vital signs were stable, but her muscle tone remained somewhat elevated. She was then re-started on a different antipsychotic medication, quetiapine, which was increased over a 7-day period to a dosage of 350 mg/d. By the 27th day of admission her psychotic symptoms showed marked reduction and her muscle tone returned to normal. After her hospital discharge, the patient took a maintenance dose of quetiapine 300 mg/d. In follow-up visits over the subsequent year, the patient's mental condition remained stable and she was able to carry out housework and basic work on the family farm.

**2. Discussion**

NMS was first reported by Deley in 1960.[1] It is a life-threatening neurologic complication associated with the use of neuroleptic agents which is characterized by a distinctive clinical syndrome of fever, muscle rigidity, autonomic nervous system dysfunction and change in mental status. NMS can occur after the use of almost any antipsychotic medication, including atypical antipsychotic medications. Previously, the reported incidence of NMS was 0.02 to 3.23% among patients taking antipsychotic medication, and the case-mortality was as high as 20 to 30% if appropriate interventions were not immediately undertaken.[2,3] In more recent reports, the estimated incidence of NMS has decreased to 0.01 to 0.02%;[4] this decrease is possibly related to increased clinical awareness of NMS, more careful prescription practices, and the wide use of atypical antipsychotic medications.[5] There are few reports about recurrent episodes of NMS, as occurred in the current case.

The occurrence of NMS is associated with patients' clinical, physical and metabolic factors, including agitation, dehydration, physical restraint, iron deficiency, and the abnormal functioning of dopamine and dopamine receptors in the central nervous system.[6] Patients usually experience physical exhaustion and dehydration before the onset of NMS. Use of high potency antipsychotic medications is more likely to precede the development of NMS than the use of low potency or atypical antipsychotic medications. The duration of treatment with antipsychotic medications and the use of excessively high doses of antipsychotic medications are not associated with the occurrence of NMS; factors that may increase the risk of NMS in individuals being treated with antipsychotic medications include the use of large parenteral doses of medication,[6] the presence of delirium,[7] and increased environmental temperature.[8]

The pathophysiology of NMS remains unclear. The mechanism of NMS appears to be related to a complicated group of neural biochemical and neuroendocrine dysfunctions. The dopamine antagonist function of antipsychotic medications is probably the trigger of NMS. In many cases, NMS is a self-limiting disease: 63% of patients recover in one week after stopping their antipsychotic medications and almost all patients recover in 30 days.[9]

The onset of NMS is usually quite rapid. A few patients may develop NMS after a single large dose of antipsychotic medication, but most develop NMS one to three days after antipsychotic treatment begins. The clinical presentation of NMS is characterized by hyperthermia, limb rigidity, tremor and autonomic instability. The autonomic nervous system symptoms include sweating, urinary retention, palpitation, rapid breathing, blood pressure instability, and salivation. Disorders of consciousness that occur during episodes of NMS include stupor, delirium and coma.[10]

Several points should be considered when treating NMS. (a) All antipsychotic medication should immediately be discontinued, supportive and symptomatic care provided, and measures to prevent or treat infections should be undertaken. The infusion of alkaline liquids (including bicarbonate) can be helpful in preventing kidney failure.[11] (b) Benzodiazepines can be administered to decrease NMS symptoms and improve prognosis. Lorazepam can be used as a first-line treatment for patients with acute NMS, especially for patients with moderately increased muscle rigidity. (c) Dopamine receptor agonists like bromocriptine mesylate and dantrolene (a muscle relaxant) can be used when attempting to reintroduce antipsychotic medications, a process that should be closely monitored. (d) Anticholinesterase drugs, like benzatropine and diphenhydramine, can be used to help achieve a balance between the two neurotransmitters in the central nervous system – acetylcholine and dopamine. (e) Electroconvulsive therapy may be helpful for patients who do not respond to medication and other supportive treatments. (f) When NMS symptoms have been controlled for two weeks, patients can resume treatment for schizophrenia, preferably with low doses of a single low-potency atypical antipsychotic medication.[12]

In the case described, the patient experienced NMS after combined treatment with haloperidol and aripiprazole (the first NMS episode) and, four years later, after combined treatment with haloperidol and clozapine (the second NMS episode). In both episodes she experienced hyperthermia, unconsciousness, muscle rigidity, difficult movement, sweating, salivation and a 10-fold increase in serum CPK. This case of recurrent NMS may be associated with the combined use of several medications or the relatively rapid increase in the dosage of antipsychotic medication. But, given that 15 to 20% of patients with NMS have had a prior episode of NMS[13] – recurrent episodes like this may also be the result of idiosyncratic genetic factors. To decrease the risk of recurrence, whenever possible patients with a history of NMS should be treated with oral preparations of a single low-potency antipsychotic medication and their dosage should be increased as slowly as possible.

## Conflict of interest

The authors report no conflicts of interest related to this manuscript.

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The patient discussed in this case report provided written informed consent for the use of the material provided in this report.

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